75. (Amended) A method according to claim 58 or 80 further comprising isolating said enzymes from said cell exhibiting an altered phenotype.

76. (Amended) A method according to claim 58 or 80 further comprising isolating said nucleic acids encoding said enzymes from said cell exhibiting an altered phenotype.

79. (Amended) A method according to claim 58 or 80, wherein said nucleic acids contain localization signals.

REMARKS

After entry of the amendments, claims 58-80 are pending in the application. Claim 80 has been added. Claims 59-76 and 79 have been amended to depend from claim 80. Support for the added claim and the accompanying amendments are found throughout the specification, particularly on pages 25-26.

No new matter is entered by way of the added claim and the amendments. Accordingly, favorable consideration of the following comments relative to the outstanding rejections as they may apply to the pending claims is respectfully requested for the reasons that follow.

Rejections Under 35 U.S.C. §101

Claims 58-79 are rejected under 35 U.S.C. §101 for lack of patentable utility. The Examiner states that the claimed methods are not supported by a specific asserted utility or a well established utility. Applicants respectfully traverse.

As the Examiner well knows, the grounds for a proper rejection based on 35 U.S.C. §101 is set forth in M.P.E.P. § 2107. Under the guidelines the Patent Office has the initial burden to show a *prima facie* case of lack of utility. See M.P.E.P. § 2107.02. The specification and the claims are to be reviewed from the perspective of one of ordinary skill in the art as to whether an applicant has asserted a specific and substantial, credible utility or a well-established utility. The applicant must provide only one credible assertion of specific and substantial utility for any claim to satisfy the utility requirement under §101. Id. Credibility is to be assessed from the

perspective of one of ordinary skill in the art in view of the evidence of record that is relevant to the Applicants assertions. Id.

The specification discloses a wide variety of specific utilities for the claimed methods. For example, the disclosure on page 42, lines 1-9 explains that the claimed methods are useful in identifying modifications of known precursors of chemotherapeutic agents to generate derivatives having anti-tumor activity. Similarly, the specification discloses introducing libraries of enzymes to alter the activities of known oncogenes in order to reverse or correct the transformed states of cells (page 42, lines 10-21). Furthermore, the specification discloses that the claimed methods are useful in modifying the toxicities of drug by reversing or protecting against the drug's toxic effects on the cells (page 52, lines 24-30). Thus, the disclosure provides ample assertions of specific and substantial, credible utility for the claimed methods.

Furthermore, Applicants submit that the claimed methods also have a well-established utility. An invention has a well established utility if a person of ordinary skill in the art would immediately appreciate why the invention is useful based on characteristics of the invention (e.g. properties of a product or obvious application of a process). The references of Khosla et al. (U.S. Pat. No. 5,672,491) and Minshull et al. (U.S. Pat. No. 5,837,458) cited by the Examiner show that introducing combinations of enzymes has the potential to change the phenotype of the cell expressing the enzymes. With this knowledge, a person skilled in the art will immediately appreciate that by expressing novel combinations of enzymes not normally active within a particular cell by use of scaffolds which bind expressed enzymes, the claimed methods also provide the capability of generating novel cellular phenotypes. Thus, in addition to a specific and substantial credible utility, Applicants submit that the claimed methods have a well-established utility.

In view of the foregoing, Applicants submit that the claimed methods drawn towards enzymes bound to scaffolds have a specific and substantial, credible utility as well as a well-established utility. Accordingly, withdrawal of the rejection of claims 58-79 under 35 U.S.C. §101 is respectfully requested.

Rejections Under 35 U.S.C. § 112, first paragraph: enablement

Claims 58-59 are also rejected under 35 U.S.C. § 112, first paragraph because the claims

are allegedly not supported by a specific and substantial utility or a well established utility. Specifically, the Examiner contends the specification lacks sufficient guidance and direction on how to screen cells for an altered phenotype, select enzymes and scaffolds, and identify the phenotypes to be detected. Given the breath of the claims, the Examiner declares undue experimentation is required to practice the claimed methods. Applicants respectfully traverse.

As a preliminary issue, the Examiner appears to suggest that the utility rejection under §101 derives from lack of a sufficiently enabling disclosure under §112, first paragraph. The M.P.E.P §2107.01(IV), however, states that a lack of utility rejection under §112, first paragraph should be made after establishing a lack of utility under §101. With due respect, it seems that the Examiner has misconceived the relationship between a rejection for lack of utility under §101 and §112, first paragraph. Moreover, the Applicants assertions of numerous specific and substantial, credible utility as well as a well-established utility satisfy the utility requirement under §101, and thus under §112, first paragraph. Accordingly, Applicants respectfully request withdrawal of the rejection under §112, first paragraph for lack patentable utility.

The Examiner also indicates a rejection under §112, first paragraph for undue breath of the claims. Although the issue appears more appropriate to a discussion of indefiniteness under §112, second paragraph, Applicants address the rejection as applied under §112, first paragraph. The Examiner cites a number of reasons for asserting that the claims are not supported by an adequate disclosure, including inadequate support for (1) screening cells for altered phenotypes, (2) selecting enzymes and scaffolds, and (3) identifying cells and phenotypes to be used.

As is well known, the specification must be enabling as to persons skilled in the art. M.P.E.P §2164.05(b). Moreover, the specification need not detail what is already well known in the art, and preferably omits such details. In re Buchner, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); see also M.P.E.P. §2164.01. Thus, standard terms and procedures need not be explained, as they will be known and interpreted by one skilled in the art.

In the first instance, the Examiner appears to suggest that the disclosure lacks guidance on screening a plurality of cells and isolating a cell with an altered phenotype. Applicants direct the Examiner to the specification on page 36, lines 5-23, which provides specific examples of identifying cells with an altered phenotypes, including changes in cell morphology, cell growth, cell viability, expression of RNAs and proteins, etc. Throughout the specification, methods of

detecting the phenotypes are described, for example on page 36, lines 24-30 and page 1-5. A skilled artisan will understand that a particular identifiable phenotype (e.g. drug toxicity) of interest will suffice as a detectable phenotype. Methods for isolating cells with a detectable phenotype are well known to those skilled in the art, including methods described in the specification on page 38, lines 20-28.

Another issue raised by the Examiner is the alleged inadequate disclosure of combinations of enzymes and scaffolds to be used in the claimed methods. Applicants direct the Examiner to the specification on page 14, lines 1-18, which describes various classes of enzymes suitable for expression. As the classes of enzymes are large and well known to those skilled in the art, a skilled artisan can select any combination of enzymes that would potentially alter the phenotype of the expressing cell. Moreover, since the claims recite expressing a library of enzymes to generate novel combinations, any combinations of enzymes or enzyme classes may be expressed. In regards to scaffolds, the disclosure states that the scaffold may comprise proteins or nucleic acids (specification, page 7). The scaffolds are modified by well known techniques to generate scaffolds containing binding sites for the enzymes.

In addition, methods for introducing and expressing scaffolds and enzymes are given in detail on page 24-31. Suitable cells are described on page 31-32 and are chosen by the skilled artisan, with cells implicated in various disease conditions particularly useful in the screens (page 31, lines 22-29). Specific cell types are also provided (page 32). As many cell types are known to those skilled in the art, the skilled artisan practicing the claimed method will select the cells appropriate to the phenotype being screened.

In view of the foregoing, Applicants submit that the claims are sufficiently supported by an enabling disclosure to satisfy the requirements under 35 U.S.C. §112, first paragraph. Accordingly, Applicants respectfully request withdrawal of the rejection.

Rejections Under 35 U.S.C. §112, first paragraph: written description

Claims 58-79 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor has possession of the claimed invention at the time the application was filed. The Examiner argues that adequate written description requires representative working

embodiments of cells, enzymes, scaffolds, and altered phenotypes. Applicants respectfully traverse.

As a preliminary matter, Applicants address the standard for written description as applied to the instant application. The Examiner contends that satisfying the written description requires representative working embodiments of a plurality of cells screened for an altered phenotype because the standards of enablement also apply to the written description requirement. This enumerated standard, however, is not the proper basis for a written description analysis. The Federal Circuit has held that the written description requirement is separate and distinct from the enablement requirement. Vas-Cath, Inc. v. Marhurkar, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991); see also M.P.E.P. §2161. The public policy rationale for the written description requirement is to "disclose in the patent sufficient information to place in the public what the inventors claim is their invention." Vas-Cath, Inc. at 1114. Accordingly, the specification is required to convey with reasonable clarity that the inventor had possession of the invention at the time of filing the application. Although a reduction to practice is one basis to show possession of the invention, the written description requirement is met by an express or inherent disclosure and may be satisfied if the "specification contains a statement of appellants invention which is as broad as appellant's broadest claims . . . ." In re Robins, 420 F.2d 452, 166 USPQ 552, 555 (CCPA 1970); see also In re Lukach, 442 F.2d 967, 969, 169 USPQ 795 (CCPA 1971); see also M.P.E.P. §2163.

Applicants submit that the specification provides sufficient detail of the claimed methods to satisfy the written description requirement. Scaffolds are described throughout the specification, particularly on page 7, with exogenous scaffolds being described specifically on page 13. Scaffolds with binding sites are described on pages 13-14 while enzymes suitable for use in the claimed method are described on page 13-14. The specification further provides for libraries of scaffolds and enzymes (page 16, lines 5-14). After introducing these enzymes and scaffolds into suitable host cells (page 24-26 and page 32), the disclosure describes screening the cells (pages 32 and 33). Specific embodiments of detectable phenotypes and screens are given throughout the specification, for example on page 36. A summary of the claimed methods is found on page 3-4.

As the foregoing illustrates, the specification provides descriptions of the identifying

characteristics of the claimed methods to amply satisfy the written description requirement. Accordingly, Applicants respectfully request withdrawal of the rejection under §112, first paragraph.

Claims 58-79 are rejected under 35 U.S.C. §112, first paragraph as improperly containing new matter. Specifically, the Examiner finds claim 58, 73 and 74 unsupported by the specification. Applicants respectfully traverse.

First, the Examiner cites a lack of support in the specification for claim 58, which according to the Examiner appears to require performing step (a) of introducing exogenous scaffolds prior to performing step (b) of introducing enzymes in the cell. The Examiner, however, suggests a construction not required or indicated in the specification. A person skilled in the art will appreciate that the scaffolds may be coexpressed or not coexpressed with the enzymes when practicing the claimed method. No particular order is prescribed by the disclosure in order to effectuate expression and interaction of the enzymes and scaffold. By imposing a particular order, the Examiner is unduly introducing limitations into the claimed subject matter. Accordingly, Applicants submit that performing step (a) and step (b) of claim 58 does not constitute new matter.

Second, the Examiner finds claim 58 lacking support in the specification for screening for an altered cell phenotype in the absence of added candidate bioactive agent precursors. Applicants direct the Examiner to page 33, lines 19-27 of the disclosure. The description states that the enzyme complex may act on an endogenous cellular compound to alter the cell phenotype. Thus, in one aspect, cells are screened for an altered phenotype without adding precursor compounds or candidate bioactive agents. Accordingly, screening of cells without adding candidate bioactive agent precursors is adequately supported in the specification.

Finally, the Examiner finds claim 73 lacking in support in the specification for isolating scaffolds from cells exhibiting an altered phenotype. In addition, the Examiner also finds claim 74 lacking support for isolating nucleic acids encoding the scaffold. Applicants direct the Examiner to the specification on page 22, lines 12-14, which states "[a] fusion partner comprising a rescue sequence may be used to purify or isolate the scaffold, enzymes or enzyme complex, or the nucleic acids encoding them." As described in the specification, "enzyme complexes" comprise scaffolds bound to cognate enzymes (page 13, lines 20-23).

Consequently, the disclosure on page 39, lines 1-13 further describes isolating the enzyme complexes by several approaches, including primers complementary to DNA regions common to the retroviral constructs or by use of rescue sequences. Alternatively, the enzyme complexes are isolated by known purification techniques (i.e. His_6 tag). Thus, claims 73 and 74 are fully supported in the disclosure.

For the reasons set forth above, Applicants submit that claims 58, 73, and 74 are fully supported by the specification. Accordingly, Applicants respectfully request withdrawal of the rejection under §112, first paragraph.

Rejections Under 35 U.S.C. §112, second paragraph

Claims 58-79 are rejected under 35 U.S.C. §112, second paragraph for omitting subject matter essential to the claimed methods. Specifically, the Examiner contends that the claims lack the essential steps of detecting a change in cell phenotype, placing cells in an environment, and/or contacting the cells with reagents needed for screening. Applicants respectfully traverse.

The Examiner argues that the step of detecting a change in cell phenotype is unclaimed essential matter. Claim 58, however, provides for "screening the plurality of cells for a cell exhibiting an altered phenotype." The specification defines an altered phenotype as any phenotypic change which is "observable, detectable, or measurable." (specification, page 36, lines 9-10). A person skilled in the art construing the claims in view of the disclosure would readily understand that screening and detecting are synonymous such that screening encompasses the step of detecting the altered phenotype. By reciting the step of screening cells for an altered phenotype, the claims expressly include detecting an altered cell phenotype.

Similarly, the step of placing cells in a medium for detecting the cell phenotype and/or contacting the cells with reagents for screening is encompassed within the screening step. A person skilled in the art appreciates that the screening conditions and reagents will depend on the phenotype being observed, detected, or measured. When direct observation of cell morphology is the basis for ascertaining altered phenotype, no screening reagent is generally required. In contrast, screening cells for cell cycle defect may use DNA binding and/or membrane binding fluorescent dyes. Consequently, the specification provides that detecting the altered phenotype will depend and correspond to the phenotype being changed (specification, page 36, lined 24-

25). A person skilled in the art of performing various assays will choose the appropriate mediums and reagents based on the phenotype being examined. As an illustrative example, the specification provides detecting an altered cellular phenotype by growing cells in selective media containing toxins, such as gentamycin, rifampicin, or ticarcillin (page 51, lines 22-29). Since claims 58-79 recite the essential step of screening cells for an altered cell phenotype, there is no failure to claim what the Applicants regard as the invention. Accordingly, Applicants respectfully request withdrawal of the rejection of claims 58-79 under §112, second paragraph.

Claim 58-79 are rejected under 35 U.S.C. 112, second paragraph for indefiniteness. Specifically, the Examiner contends claim 58 fails to recite any nucleic acid or amino acid sequences of specific enzymes. Applicants respectfully traverse.

Applicants respectfully remind the Examiner that definiteness of claim language must be analyzed in view of the content of the application disclosure, the teachings of the prior art, and in regard to the knowledge of those skilled in the art. M.P.E.P §2173.01. Moreover, the guidelines provide for some lattitude in the manner of expression even though the claim language is not as precise as that desired by the Examiner as long as the claims set out and circumscribe the claimed subject matter with a reasonable degree of clarity and particularity. M.P.E.P §2173.02. Thus, breath of a claim does not render a claim indefinite. In re Miller, 169 USPQ 597 (CCPA 1971).

As is well known by those skilled in the art, enzymes define a rather large class of proteins and nucleic acids with identified functions. The specification provides a catalog of exemplary types of enzymes suitable for the claimed methods (see specification, page 14, lines 1-19). Since the claimed methods recite introducing into cells a library of enzymes, a person skilled in the art can express a variety of enzymes to generate novel combinations capable of producing an altered cellular phenotype. A skilled artisan practicing the claimed methods may or may not restrict the library of enzymes to particular classes of enzymes, and may include all or part of nucleic acids or protein sequences (see specification, page 14, lines 19-22). Thus, enzymes are defined in language as precise the subject matter permits. Applicants submit that given the scope of suitable enzymes, requiring recitation of specific nucleic acid or amino acid sequences is beyond what is required under §112, second paragraph. Accordingly, Applicants respectfully request withdrawal of the rejection of claims 58-79 under § 112, second paragraph.

Claim 59 is rejected for indefiniteness because the term "exogenous bioactive agent precursors" is not adequately described. The Examiner suggests that "exogenous bioactive agent" is ambiguous in distinguishing between components of the growth medium from candidate bioactive agent precursor. Applicants respectfully traverse.

Claim 59 recites, in part, contacting cells with a candidate bioactive agent prior to screening cells for an altered phenotype. A person skilled in the art will understand this to mean that the phenotype of the cell expressing the nucleic acid libraries is examined in a condition lacking a bioactive agent precursor relative to a condition containing the bioactive agent precursor. The distinction is not between whether the precursor constitutes the growth medium, but rather between the phenotypes expressed in the presence or absence of candidate bioactive precursors, regardless of whether these precursors are nutrients, growth factors or some other organic compound. Consequently, requiring a distinction between nutrients in the growth medium and candidate bioactive agent precursor misconstrues the nature of the claimed subject matter.

In view of the foregoing, Applicants submit that "exogenous candidate precursor" is defined with a reasonable degree of clarity and particularity to apprise those skilled in the art as to the scope of the claimed subject matter. Accordingly, Applicants respectfully request withdrawal of the rejection of claim 59 under §112, second paragraph.

Claim 65 is rejected for indefiniteness because the term "targeting sequence" is allegedly ambiguous as to what it excludes and includes. In particular, the Examiner argues that binding sites on scaffolds appears to encompass targeting sequences. Further, the Examiner suggest a lack of clarity in distinguishing between a targeting signal and a localization signal.

Applicants direct the Examiner to the specification on page 16, lines 11-20 for descriptions of targeting sequences. The scope of targeting sequences encompass binding sequences that allow binding of an expression product to a particular molecule or class of molecules, sequences that allow for selective degradation, and localization sequences that localize an expression product to particular subcellular or extracellular compartments. As is well known by those skilled in the art, numerous classes of sequences are known that allow binding of a protein to a particular molecule, such as other proteins. Since these sequences are also useful as binding sites on scaffolds for binding enzymes, binding site may also comprise

targeting sequences. Thus, multiple functions are attributable to targeting sequences and may be adapted by the skilled artisan to other uses.

As the Examiner is well aware, the "requirement for clarity and precision must be balanced with the limitations of the language and the science." M.P.E.P. §2173.05(a). Consequently, given the variety of classes of targeting sequences and their potential multiple uses, the claimed method sufficiently defines targeting sequences with reasonable clarity and particularity, and within the limitations of the language and the science, to reasonably apprise those skilled in the art as to the scope of the claimed method. Accordingly, Applicants respectfully request withdrawal of the rejection of claim 65 under §112, second paragraph.

Claim 66 is rejected for indefiniteness because the Examiner finds the scope of "rescue sequence" of the claim is inadequately defined. Applicants respectfully traverse.

Applicants direct the Examiner to the specification on page 22, lines 13-19, which defines fusion partners comprising rescue sequences. The customary and ordinary meaning of fusion partners as used by those skilled in the art are nucleic acids or amino acid sequences fused to other nucleic acid or amino acid sequences to generate a fusion product, which is distinguished from native nucleic acid sequences or the native amino acid sequence. The specification further defines fusion partners as a sequence that confers a common functionality or ability to a nucleic acid or the expression product. The common functionality of rescue sequences, which are fusion partners, allows purifying or isolating the scaffolds, enzymes, or enzyme complexes, or the nucleic acids encoding them.

Given the definition of fusion partners and rescue sequences, amino acid sequences in a fusion construct capable of reacting with an antibody constitutes, by definition, a rescue sequence. Similarly, unique nucleic acid sequences of a fusion nucleic acid that allows isolation of the nucleic acid of interest is encompassed within the "rescue sequence" of the claims. In view of the content of the disclosure and the knowledge of those skilled in the art, Applicants submit that "rescue sequence" is defined with sufficient clarity and particularity to apprise those skilled in the art as to the scope of claim 66. Accordingly, Applicants respectfully request withdrawal of the rejection of claim 66 under §112, second paragraph.

Claim 67 is rejected for indefiniteness because the Examiner contends the scope of "stability sequence" is ambiguous. Applicants respectfully traverse.

The specification describes stability sequence as a sequence conferring stability to the "expression products or the nucleic acids encoding them." (page 22, lines 23-24). As is well known in the art, various sequences are known to increase half-life or limit degradation of nucleic acids or proteins, including 5' or 3' untranslated regions, polyadenylation sites, and 5' CAP structures. A person skilled in the art of nucleic acids (or proteins) will also understand that many of these sequences are elements having other physiological functions, such as allowing efficient expression of nucleic acids. Although endowed with multiple cellular functions, such sequences by limiting degradation or increasing half-life of the expressed product describes the properties encompassed within the definition of stability sequence. That is, the sequence stabilizes the expressed product within the cell.

Thus, Applicants submit that "stability sequence" when read in light of the specification reasonably apprises those skilled in the art as to the scope of the claimed method in language as precise as permitted by the known properties of stabilizing sequences. Accordingly, Applicants respectfully request withdrawal of the rejection of claim 67 under §112, second paragraph.

Rejections under 35 U.S.C. §102(e)

Claims 58, 59-62, 64-66, 68, 69, 72, 77 and 78 are rejected under 35 U.S.C. §102(e) as anticipated by Khosla et al. (U.S. Pat. No. 5,672,491) (hereinafter "Khosla"). Applicants respectfully traverse.

As a preliminary issue, Applicants address certain interpretations of Khosla *et al.* asserted by the Examiner. Khosla teach the synthesis of polyketides by 6-deoxyerythronolide B synthetase (DEBS), a polyketide synthase (PKS) consisting of three different proteins, eryA1, eryA2, and eryA3. The authors construct expression vectors encoding these three proteins, introduce them into host cells having deletions of the PKS "gene cluster," and demonstrate that polyketides are made by combined action of the replacement genes. From this description, the Examiner asserts that Khosla disclose expression of "exogenous scaffolds" and "at least two enzymes," which interact with an exogenous scaffold. This conclusion derives from characterization of polyketide synthase as a "multi-enzyme complex" whereby one of the synthase enzymes acts equivalent to an "exogenous scaffold" by interacting with the other two synthase enzymes, thus describing the scaffolds and enzymes of the claimed method. Khosla,

however, describes PKS as "assemblies of several large multifunctional enzymes" without indicating how the subunits are arranged in the assembly. Multifunctionality of PKS relates to the presence of numerous catalytic active sites (e.g. clusters or modules) within a single polypeptide of PKS rather than a description of a physically interacting "multi-enzyme" complex. A thorough reading of Khosla reveals no express description of physical arrangements of the PKS enzymes.

Since Khosla fail to expressly describe introducing nucleic acids encoding scaffolds and enzymes, the Examiner appears to base the anticipation rejection on inherency. In other words, since the enzymes for polyketide biosynthesis allegedly physically interact *in vivo*, expressing the PKS subunits inherently describes an enzyme acting as an exogenous scaffold, which binds to a first and a second enzyme.

Under inherency, a disclosure that does not describe the elements of a claim can still anticipate if the missing descriptive matter is necessarily present in the thing described in the reference and that it would be so recognized by one of ordinary skill in the art. In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). Inherency, however, may not be established by probabilities or possibilities. Id. at 1950. There mere fact that a certain thing may result from a given set of circumstances is not sufficient. Id. In regards to method claims, the accidental or unwitting achievement of that result does not constitute anticipation. In re Marshall, 578 F.2d 301, 198 USPQ 344 (CCPA 1978).

Applicants submit that the Examiner has not proffered a satisfactory basis to establish inherency. Khosla fail to specifically show that PKS enzymes physically interact *in vivo* according to the arrangement recited in the instant claims since the art of record is void of such evidence, other than a description of an "assembly of multifunctional enzymes." At best, Khosla show that expression of the polyketide synthase enzymes encoded by a "replacement PKS gene cluster" in a *S. coelicolor* deleted for PKS genes results in synthesis of polyketides. Absent knowledge of physical interactions between enzymes, there is no showing that expressing the enzymes *in vivo* result in the interactions described in the claimed methods. As is well known in the art, unknown endogenous factors are sometimes required for proteins to interact *in vivo*. Thus, the asserted physical interactions between eryA1, eryA2, and eryA3 are not supported by the evidence of record. In the absence this knowledge, a person skilled in the art would not

recognize or conclude that expressing the three PKS enzymes in a cell would give rise to *in vivo* interactions where one enzyme acts as a scaffold for the other expressed enzymes. Accordingly, inherency has not been established.

In addition, the Examiner contends that since Khosla disclose eight different enzymes of the polyketide pathway as possible constituents of a "replacement polyketide gene cluster," the reference allegedly teaches a "scaffold" with at least three, four, or five binding sites as recited in claims 60, 61 and 62, respectively. The art of record, however, provides no description that any of the described enzymes act as a scaffold with binding sites for three, four or five other enzymes. These structural relationships purported to occur *in vivo* is merely a suggestion of the possibility that at least one of the described enzymes has the properties recited in the claimed methods. No extrinsic evidence is provided to show that the enzymes inherently interact *in vivo* in the manner described by the Examiner.

Moreover, expressing other enzymes of the polyketide synthetic pathway does not necessarily result in enzyme combinations where one enzyme acts as a scaffold for at least a first and a second enzyme of the metabolic pathway. In the absence of knowledge that an enzyme interacts with other enzymes, whether an enzyme selected for expression acts as a scaffold will depend merely on chance that the selected enzyme binds the other expressed enzymes. The probability of this happening decreases in relation to the increase in the number of enzymes involved in the metabolic pathway. Consequently, a combination comprising a scaffold which binds at least a first and a second enzyme does not necessarily result from expressing any combination of PKS enzymes such as described in Khosla. This accidental or unwitting practice cannot constitute anticipation by inherency.

In view of the foregoing, Applicants submit that Khosla do not teach each and every element of the claimed method, either expressly or inherently, and thus fail to anticipate the recited claims. Accordingly, Applicants respectfully request withdrawal of the rejection under §102(e) over Khosla.

Claims 58, 59, 63-70, and 74-79 are rejected under 35 U.S.C. § 102(e) as anticipated by Minshull et al. (U.S. Patent No. 5,837,458) (hereinafter "Minshull") with reference to Srere, P.A. (1987) Ann. Rev. Biochem. 56: 89-91 (hereinafter "Srere") as supporting the inherency of "scaffolds." Applicants respectfully traverse.

As a preliminary matter, the Examiner has provided only the first two pages of Srere rather than the providing a complete text of the prior art reference as required under 37 CFR § 1.104, thus limiting Applicants' opportunity to fully consider the issues raised in rejection of the claims.

In regards to the merits of the rejection, the Examiner suggests that since Minshull disclose introducing and expressing altered (i.e. by recursive sequence recombination) genes or gene clusters encoding enzymes of metabolic pathways, Minshull anticipates the claimed methods by virtue of scaffolds inherent in the multienzyme complexes that comprise parts of many metabolic pathways. Srere is provided as extrinsic evidence showing inherency of scaffolds. Applicants submit that Minshull fail to anticipate the claimed methods for a several of reasons.

Minshull do not expressly teach expression of enzymes which explicitly physically interact, but rather teach expression of enzymes acting in particular metabolic pathways. Specific embodiments given in Minshull include expression of altered polyketide gene clusters (column 6, lines 59-67), individual enzymes involved in polyketide synthesis (column 7, lines 28-43), multisubunit diooxygenase (column 7, lines 15-27), PAH degradating gene cluster, first two enzymes of atrazine metabolism, nitroreductases, macrolide biosynthetic pathways (i.e. penicillin, cephalosporin). Minshull do not expressly show that these enzymes bind to other enzymes sufficiently to be identified as a scaffold. Although the Examiner argues that polyketide enzymes are joined together by noncovalent interactions, there is no description in Minshull of such interactions.

The extrinsic evidence of Srere do describe multienzyme complexes. However, a vague reference to expressing all enzymes in a pathway fails to provide sufficient evidence showing which components interact to satisfy the limitations of the claims. Mere isolation or demonstration of multienzyme complexes is insufficient to provide information as to which enzymes act as scaffold for other enzymes of the metabolic pathway.

Moreover, Minhsull fail to anticipate the claimed methods based on inherency since expressing enzymes of a metabolic pathway merely engenders a probability that one of the expressed enzymes will act as a scaffold. As discussed for Khosla, absent knowledge that a particular enzyme binds other known enzymes, a person following Minshull may choose

combinations of enzymes comprising part of the metabolic pathway but which do not interact in the manner of the claimed method. Consequently, expressing enzymes of the metabolic pathway only creates the probability or possibility that the combination will generate the claimed scaffolds and enzymes. As discussed above, an accidental or unwitting practice does not constitute anticipation by inherency.

In view of the foregoing, Applicants submit that Minshull fail to teach each and every element, either expressly or inherently, and thus fail to anticipate claims 58, 59, 63-70, and 74-79. Accordingly, Applicants respectfully request withdrawal of the rejections under §102(e) over Minshull.

Rejections Under 35 U.S.C § 103(a)

Claims 71 and 73 are rejected under 35 U.S.C. §103(a) as being rendered obvious over Minshull, et al. (U.S. Pat. No. 5,837,458). The Examiner appears to conclude that neither Khosla nor Minshull teach each and every element of claim 71 or 73 to anticipate the claimed methods. Thus, the rejection of claim 71 under § 103(a) over Minshull is based on the motivation by one skilled in the art to introduce and express via retroviral vectors nucleic acids encoding altered enzymes of metabolic pathways. Further, the Examiner urges that a person skilled in the art would have been motivated to isolate and characterize the enzyme acting as the scaffold, as recited in claim 73. Applicants respectfully traverse.

Minshull disclose various methods for introducing nucleic acids encoding enzymes into cells to generate enzymes having altered activities. These methods include plasmid and bacteriophage mediated nucleic acid delivery. There is no teaching or suggestion in Minshull of using retroviral vectors for delivery of nucleic acids encoding scaffolds or enzymes.

When rejecting claims under 35 U.S.C. § 103, the Examiner bears the burden of establishing a *prima facie* case of obviousness. In re Bell, 26 USPQ2d 1529 (Fed. Cir. 1993); M.P.E.P. § 2142. To establish a *prima facie* case, three basic criteria must be met: (1) the prior art must provide one of ordinary skill with a suggestion or motivation to modify or combine the teachings of the references relied upon by the Examiner to arrive at the claimed invention; (2) the prior art must provide one of ordinary skill with a reasonable expectation of success; and (3) the prior art, either alone or in combination, must teach or suggest each and every limitation of

the rejected claims. The teaching or suggestion to make the claimed invention, as well as the reasonable expectation of success, must come from the prior art, not Applicant's disclosure. In re Vaeck, 20 USPQ2d 1438 (Fed. Cir. 1991); M.P.E.P. § 706.02(j). If any one of these criteria is not met, *prima facie* obviousness is not established. Moreover, obviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established. In re Rijckaert, 9 F.2d 1531, 28 USPQ2d 1955 (Fed. Cir. 1993).

As Minshull fail to teach or suggest expression of scaffolds and their introduction into cells via retroviral vectors, Minshull do not provide the necessary motivation to use retroviral vectors for delivery of nucleic acids encoding scaffolds and enzymes, which bind at least a first and second enzyme. The Examiner suggests that the motivation arises from expressing multienzyme complexes whereby at least one of the enzymes act as a scaffold to bind other enzymes. The art of record, however, provides no evidence for knowledge of specific interactions between enzymes that meet the limitations in the claimed methods. Allusions to multienzyme complex fails to define which enzymes should be expressed to provide a scaffold for other enzymes, unless there is some knowledge of the structural relationships between the enzymes in the metabolic pathway. It would not have been obvious to express an enzyme acting as a scaffold if such knowledge did not exist at the time the invention was made. In this sense, Minshull fail to render obvious claims 71 and 73 since there is no teaching or suggestion to use retroviral vectors to express scaffolds and express enzymes which bind to the scaffolds. Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §103(a).

CONCLUSION

The Applicants submit that all pending claims of the instant application are in compliance with all the requirements of patentability and are in condition for allowance. Accordingly, early notification of such allowance is earnestly solicited.

Attached hereto is a marked up version of the changes made to the claims by the AMENDMENT AND REPLY TO OFFICE ACTION." The attached page is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE. In addition, an Appendix of

the pending claims is attached for the Examiner's convenience.

If after review, the Examiner feels there are further unresolved issues or determines that prosecution of the above reference application would benefit from a telephone interview, the Examiner is invited to call the undersigned attorney at (415) 781-1989.

Respectfully submitted,

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MARKED UP VERSION TO SHOW CHANGES MADE

59. (Amended) The method of claim 58 or 80, further comprising contacting said cells, prior to said screening, with a library of exogenous bioactive agent precursors.

60. (Amended) A method according to claim 58 or 80, wherein each said scaffold comprises at least three binding sites.

61. (Amended) A method according to claim 58 or 80, wherein each said scaffold comprises at least four binding sites.

62. (Amended) A method according to claim 58 or 80, wherein each said scaffold comprises at least five binding sites.

63. (Amended) A method according to claim 58 or 80, wherein said cells are mammalian cells.

64. (Amended) A method according to claim 58 or 80, wherein said scaffolds are linear.

65. (Amended) A method according to claim 58 or 80, wherein said library of nucleic acids encoding a library of exogenous scaffolds further comprises at least one targeting sequence.

66. (Amended) A method according to claim 58 or 80, wherein said library of nucleic acids encoding a library of exogenous scaffolds further comprises at least one rescue sequence.

67. (Amended) A method according to claim 58 or 80, wherein said library of nucleic acids encoding a library of exogenous scaffolds further comprises at least one stability sequence.

68. (Amended) A method according to claim 58 or 80, wherein said library of nucleic acids encoding at least a first enzyme and a second enzyme further comprises at least one targeting

sequence.

69. (Amended) A method according to claim 58 or 80, wherein said library of nucleic acids encoding at least a first enzyme and a second enzyme further comprises at least one rescue sequence.

70. (Amended) A method according to claim 58 or 80, wherein said library of nucleic acids encoding at least a first enzyme and a second enzyme further comprises at least one stability sequence.

71. (Amended) A method according to claim 58 or 80, wherein said introducing comprises retroviral infection.

72. (Amended) A method according to claim 58 or 80, wherein said method further comprises isolating said cell exhibiting an altered phenotype.

73. (Amended) A method according to claim 58 or 80 further comprising isolating said scaffold from said cell exhibiting an altered phenotype.

74. (Amended) A method according to claim 58 or 80 further comprising isolating said nucleic acid encoding said scaffold from said cell exhibiting an altered phenotype.

75. (Amended) A method according to claim 58 or 80 further comprising isolating said enzymes from said cell exhibiting an altered phenotype.

76. (Amended) A method according to claim 58 or 80 further comprising isolating said nucleic acids encoding said enzymes from said cell exhibiting an altered phenotype.

79. (Amended) A method according to claim 58 or 80, wherein said nucleic acids contain localization signals.

The following new claim has been added:

80. (New) A method of screening a plurality of cells, comprising:

a) producing a plurality of cells comprising a library of nucleic acids encoding a library of exogenous scaffolds;

b) introducing into said plurality of cells a library of retroviral vectors comprising nucleic acids each encoding at least a first enzyme and a second enzyme; and

c) screening said plurality of cells for a cell comprising at least one exogenous scaffold and exhibiting an altered phenotype,

wherein each of said scaffolds comprises at least a first binding site and a second binding site, and wherein said first enzyme binds to said first binding site and said second enzyme binds to said second binding site.

APPENDIX OF PENDING CLAIMS

58. A method of screening a plurality of cells, comprising:

a) producing a plurality of cells comprising a library of nucleic acids encoding a library of exogenous scaffolds;

b) introducing into said plurality of cells a library of nucleic acids each encoding at least a first enzyme and a second enzyme; and

c) screening said plurality of cells for a cell comprising at least one exogenous scaffold and exhibiting an altered phenotype,

wherein each of said scaffolds comprises at least a first binding site and a second binding site, and wherein said first enzyme binds to said first binding site and said second enzyme binds to said second binding site.

59. (Amended) The method of claim 58 or 80, further comprising contacting said cells, prior to said screening, with a library of exogenous bioactive agent precursors.

60. (Amended) A method according to claim 58 or 80, wherein each said scaffold comprises at least three binding sites.

61. (Amended) A method according to claim 58 or 80, wherein each said scaffold comprises at least four binding sites.

62. (Amended) A method according to claim 58 or 80, wherein each said scaffold comprises at least five binding sites.

63. (Amended) A method according to claim 58 or 80, wherein said cells are mammalian cells.

64. (Amended) A method according to claim 58 or 80, wherein said scaffolds are linear.

65. (Amended) A method according to claim 58 or 80, wherein said library of nucleic acids encoding a library of exogenous scaffolds further comprises at least one targeting sequence.

66. (Amended) A method according to claim 58 or 80, wherein said library of nucleic acids encoding a library of exogenous scaffolds further comprises at least one rescue sequence.

67. (Amended) A method according to claim 58 or 80, wherein said library of nucleic acids encoding a library of exogenous scaffolds further comprises at least one stability sequence.

68. (Amended) A method according to claim 58 or 80, wherein said library of nucleic acids encoding at least a first enzyme and a second enzyme further comprises at least one targeting sequence.

69. (Amended) A method according to claim 58 or 80, wherein said library of nucleic acids encoding at least a first enzyme and a second enzyme further comprises at least one rescue sequence.

70. (Amended) A method according to claim 58 or 80, wherein said library of nucleic acids encoding at least a first enzyme and a second enzyme further comprises at least one stability sequence.

71. (Amended) A method according to claim 58 or 80, wherein said introducing comprises retroviral infection.

72. (Amended) A method according to claim 58 or 80, wherein said method further comprises isolating said cell exhibiting an altered phenotype.

73. (Amended) A method according to claim 58 or 80 further comprising isolating said scaffold from said cell exhibiting an altered phenotype.

74. (Amended) A method according to claim 58 or 80 further comprising isolating said nucleic acid encoding said scaffold from said cell exhibiting an altered phenotype.

75. (Amended) A method according to claim 58 or 80 further comprising isolating said enzymes from said cell exhibiting an altered phenotype.

76. (Amended) A method according to claim 58 or 80 further comprising isolating said nucleic acids encoding said enzymes from said cell exhibiting an altered phenotype.

77. (Amended) A method according to claim 59, wherein said altered phenotype is due to the presence of one or more of said bioactive agent precursors.

78. (Amended) A method according to claim 77 further comprising identifying said one or more bioactive agents.

79. (Amended) A method according to claim 58 or 80, wherein said nucleic acids contain localization signals.

80. (New) A method of screening a plurality of cells, comprising:

a) producing a plurality of cells comprising a library of nucleic acids encoding a library of exogenous scaffolds;

b) introducing into said plurality of cells a library of retroviral vectors comprising nucleic acids each encoding at least a first enzyme and a second enzyme; and

c) screening said plurality of cells for a cell comprising at least one exogenous scaffold and exhibiting an altered phenotype,

wherein each of said scaffolds comprises at least a first binding site and a second binding site, and wherein said first enzyme binds to said first binding site and said second enzyme binds to said second binding site.